Food and Drug Administration
Center for Drug Evaluation and Research

Final Summary Minutes of the Anesthetic and Analgesic Drug Products Advisory Committee Meeting January 16, 2020

Location: FDA White Oak Campus, Building 31 Conference Center, The Great Room (Rm. 1503), 10903 New Hampshire Ave, Silver Spring, Maryland.

Topic: The committee discussed new drug application (NDA) 204803, bupivacaine extended-release solution for instillation, submitted by DURECT Corp., for the proposed indication of post-surgical analgesia. The committee discussed whether the Applicant adequately demonstrated the safety and efficacy of bupivacaine extended-release solution for post-surgical analgesia and the appropriateness of the proposed patient populations. The committee also was asked to discuss the approvability of this product.

These summary minutes for the January 16, 2020 meeting of the Anesthetic and Analgesic Drug Products Advisory Committee of the Food and Drug Administration were approved on March 3, 2020.

I certify that I attended the January 16, 2020 meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/	**/s/**
Moon Hee V. Choi, PharmD	Ronald S. Litman, DO, ML
Designated Federal Officer, AADPAC	Chairperson, AADPAC

Final Summary Minutes of the Anesthetic and Analgesic Drug Products Advisory Committee Meeting
January 16, 2020

The Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) of the Food and Drug Administration, Center for Drug Evaluation and Research, met on January 16, 2020, at the FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503), 10903 New Hampshire Avenue, Silver Spring, Maryland. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA and DURECT Corp. The meeting was called to order by Ronald S. Litman, DO, ML (Chairperson). The conflict of interest statement was read into the record by Moon Hee V. Choi, PharmD (Designated Federal Officer). There were approximately 85 people in attendance on January 16, 2020. There were three Open Public Hearing presentations.

A verbatim transcript will be available, in most instances, at approximately ten to twelve weeks following the meeting date.

Agenda:

The committee discussed new drug application (NDA) 204803, bupivacaine extended-release solution for instillation, submitted by DURECT Corp., for the proposed indication of post-surgical analgesia. The committee discussed whether the Applicant adequately demonstrated the safety and efficacy of bupivacaine extended-release solution for post-surgical analgesia and the appropriateness of the proposed patient populations. The committee also was asked to discuss the approvability of this product.

Attendance:

Anesthetic and Analgesic Drug Products Advisory Committee Members Present (Voting): Basavana G. Goudra, MD, FRCA, FCARSCI; Jennifer Higgins, PhD (Consumer Representative); Ronald S. Litman, DO, ML (Chairperson); Maura S. McAuliffe, CRNA, MSN, MSNA, PhD, FAAN; Mary Ellen McCann, MD, MPH; Abigail B. Shoben, PhD; Kevin L. Zacharoff, MD, FACIP, FACPE, FAAP; Lonnie Zeltzer, MD

Anesthetic and Analgesic Drug Products Advisory Committee Member Present (Non-Voting): Jay Horrow, MD, MS, FACC (Industry Representative)

Anesthetic and Analgesic Drug Products Advisory Committee Members Not Present (Voting): Maryam Jowza, MD; Michael Sprintz, DO, DFASAM; Richard D. Urman, MD, MBA

Temporary Members (Voting): Joseph J. Cullen, MD; Edward Falta, MD, FACS; Joseph O'Brien, MBA (Patient Representative); Sherif Zaafran, MD, FASA

FDA Participants (Non-Voting): Rigoberto Roca, MD; Naomi Lowy, MD; Martha A. Van Clief, MD; Renee Petit-Scott, MD; Katherine Meaker, MS

Designated Federal Officer (Non-Voting): Moon Hee V. Choi, PharmD

Open Public Hearing Speakers Present: Stephanie Fox-Rawlings, PhD (National Center for Health Research); Janice Burt; Nancy Guild

The agenda was as follows:

Call to Order and Introduction of Committee	**Ronald S. Litman, DO, ML** Chairperson, AADPAC
Conflict of Interest Statement	**Moon Hee V. Choi, PharmD** Designated Federal Officer, AADPAC
FDA Opening Remarks	**Rigoberto Roca, MD** Acting Division Director Division of Anesthesiology, Addiction Medicine and Pain Medicine (DAAP) Office of Neuroscience (ON) Office of New Drugs (OND), CDER, FDA
APPLICANT PRESENTATIONS	**DURECT Corporation**
Clinical Context	**Tong J. Gan, MD, MHS, FRCA, MBA** Professor and Chairman Department of Anesthesiology Stony Brook School of Medicine
Introduction to Clinical Program	**Neil Verity, PhD** Executive Director, Pharmacology Project Leader and Principal Scientist DURECT Corporation
Efficacy and Safety	**Jon Meisner, MD** Sr. Medical Director, Medical Affairs DURECT Corporation
General Surgeon's Perspective	**Asok Doraiswamy, MD, FACS** General Surgeon Methodist Hospital of Southern California Huntington Memorial Hospital
Anesthesiologist's perspective	**Harold Minkowitz, MD** Anesthesiologist Memorial Hermann Katy Hospital Memorial Hermann Memorial City Medical Center

Clarifying Questions

BREAK

FDA PRESENTATIONS

Current Postsurgical Analgesic Treatment Options & Summary of Clinical Development Program	**Renee Petit-Scott, MD** Medical Officer DAAP, ON, OND, CDER, FDA
Statistical Review of Efficacy Data	**Katherine Meaker, MS** Statistics Reviewer Division of Biometrics I, Office of Biostatistics Office of Translational Sciences, CDER, FDA
Clinical Implications of Efficacy Data	**Renee Petit-Scott, MD**
Assessment of Safety Data from Studies Submitted in Support of NDA	**Renee Petit-Scott, MD**

Clarifying Questions

LUNCH

OPEN PUBLIC HEARING

Charge to the Committee	**Rigoberto Roca, MD**

Questions to the Committee/Committee Discussion

BREAK

Questions to the Committee/Committee Discussion

ADJOURNMENT

Questions to the Committee:

1. **DISCUSSION:** Discuss whether the Applicant has provided sufficient information to support the proposed indication.

   Committee Discussion: *The Committee members expressed confusion with the Applicant's presentation of a pivotal study to support approval of Posimir, noting that the presentation was not the same pivotal study (i.e., PERSIST C803-028) previously sent to the Committee*

members in the FDA briefing materials. The majority of the Committee members agreed that the Applicant did not provide sufficient information to support the proposed indication. These Committee members suggested that a future study could minimize and/or standardize intra-operative narcotic administration and evaluate time to first dose post-operatively. Additionally, some members noted that surgical procedures utilizing either a regional or neuraxial anesthetic technique (thereby avoiding administration of general anesthesia) would further inform the safety profile of the proposed drug product. Some Committee members expressed the need for clarification of the drug instillation process and what, if any, specific devices may be needed for correct administration. One Committee member stated that there were significant limitations in the data presentations and noted the visual displays, including data figures, were misleading to the observer. Please see the transcript for details of the Committee's discussion.

2. **DISCUSSION:** Discuss whether there are issues with this Complete Response resubmission that warrant additional studies and, if so, should these studies be conducted before or after approval.

   Committee Discussion: *Some Committee members expressed difficulty in comparing data from studies evaluating different surgical procedures, which have different pain responses and variable local anesthetic responses. Several Committee members stated the need for a study to evaluate the risks associated with unintentional intravenous injection (as accidental intravenous administration could happen in the operating room) and suggested this study could be conducted post-approval. Please see the transcript for details of the Committee's discussion.*

3. **DISCUSSION:** Discuss whether the efficacy, safety, and overall risk-benefit profile of Posimir support the approval of this application.

   Committee Discussion: *The Committee members had mixed opinions on whether the efficacy, safety, and overall risk-benefit profile of Posimir supported the approval of this application. Some Committee members stated that the efficacy data presented was not statistically, nor clinically, meaningful, and thus did not support approval of this application. However, other Committee members noted that short-term efficacy was demonstrated and the drug product could be beneficial in certain surgical populations (such as caesarean section or inguinal hernia repair) and could perhaps serve as an alternative to opioid analgesics. One Committee member expressed concern with the incidence and size of the post-procedural contusions and the associated risks to specific subgroups of patients, including those with cancer, diabetes, or in an immunocompromised state. Please see the transcript for details of the Committee's discussion.*

4. **VOTE:** Do you recommend approval of Posimir, bupivacaine extended-release solution, 660 mg/5 mL (132 mg/mL), for the proposed indication of single-dose instillation into the surgical site to produce post-surgical analgesia?

   a. If you voted "Yes," please discuss the rationale for your vote and specify whether any post-approval studies should be required.

b. If you voted "No," please discuss the rationale for your vote and what additional data are needed for approval.

Vote Result: Yes: 6 No: 6 Abstain: 0

***Committee Discussion**: The Committee members were split on whether they recommend approval of Posimir, bupivacaine extended-release solution, 660 mg/5 mL (132 mg/mL), for the proposed indication of single-dose instillation into the surgical site to produce post-surgical analgesia. The Committee members who voted "Yes" agreed that short-term efficacy, including a reduction in post-operative opioid use, was demonstrated, and that the product could be an alternative to opioid analgesia. Some members recommended a post-approval study to evaluate inadvertent intravenous administration. Some members also expressed the need for a better delivery vehicle or device, or a single-use package including the drug product and delivery device. The Committee members who voted "No" generally agreed that efficacy was not demonstrated in the surgical populations evaluated. These members recommended an additional evaluation of the safety risks associated with the surgical wound and they also recommended a study to evaluate inadvertent intravenous administration. Committee members agreed that the clinical studies included in the drug product's labeling will inform how the product is marketed and also inform expectations regarding the duration of efficacy. Please see the transcript for details of the Committee's discussion.*

The meeting was adjourned at approximately 2:46 p.m.